AMENDMENTS TO THE CLAIMS

Listing of the Claims

This listing replaces all prior versions and listings of claims in the application.

1.-62. (Canceled)

63. (Currently amended) A monoclonal antibody or a functional fragment thereof, ~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms, ~~and which~~ binds to TRAIL-R2, and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody or [[and]] the functional fragment thereof.

64. (Currently amended) A monoclonal antibody or a functional fragment thereof, ~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms, ~~and which~~ binds to TRAIL-R2, and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody or [[and]]the functional fragment thereof, and wherein the survival rate of said carcinoma cells in the following test using the said antibody or functional fragment thereof is 80% or less,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which are colon carcinoma cells, at a concentration of 1.0×10^5/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the antibody or the functional fragment thereof which is bound binds to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that the concentration of the antibody or the functional fragment thereof becomes 1000ng/ml when it is added to each well at 10μl/well, culturing each well at 37°C under 5.0% carbon dioxide gas for 48 hours, washing each well once with PBS and adding fresh RPMI-1640 medium containing 10% FCS at100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQUEOUS Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) as well as a carcinoma cell-free well and a well containing said carcinoma cells and a control antibody which does not bind to said carcinoma cells and is the same subclass as the antibody or the functional fragment thereof which binds to TRAIL-R2 or a well containing said carcinoma cells and a control antibody which does not bind to said carcinoma cells and does not have a constant region using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is ~~calculates~~ calculated using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing said carcinoma cells and the antibody or the functional fragment thereof, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents (i) the measured value of the absorbance of a well containing said carcinoma cells and a control antibody which does not bound bind to said carcinoma cells and is the same subclass as the antibody or the functional fragment thereof bound which binds to TRAIL-R2 when the antibody or the functional fragment thereof has a constant region, or (ii) the measured value of a well containing said carcinoma cells and a control antibody which does not bound bind to said carcinoma cells and does not have a constant region when the antibody or the functional fragment thereof does not have a constant region).

65. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 64, wherein the survival rate is 60% or less.

66. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 64, wherein the survival rate is 40% or less.

67. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 64, wherein the survival rate is 20% or less.

68. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 64, wherein the survival rate is 10% or less.

69. (Currently amended) A monoclonal antibody or a functional fragment thereof, ~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms, ~~and which~~ binds to TRAIL-R2, and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody or [[and]] the functional fragment thereof, and wherein the survival rate of said carcinoma cells in the following test using the said antibody is 80% or less,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which are colon carcinoma cells, at a concentration of 1.0×10^5/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the antibody or the functional fragment thereof which is bound binds to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that the concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing each well at 37°C under 5.0% carbon dioxide gas for 48 hours, washing each well once with PBS and adding fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQUEOUS Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) as well as a carcinoma cell-free well and a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody which binds to TRAIL-R2 and does not bind to the carcinoma cells using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is ~~calculates~~ calculated using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing said carcinoma cells, "b" represents the measured value of a carcinoma cell-free well, and "c" represents the measured value of a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells).

70. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 69, wherein the survival rate is 60% or less.

71. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 69, wherein the survival rate is 40% or less.

72. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 69, wherein the survival rate is 20% or less.

73. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 69, wherein the survival rate is 10% or less.

74. (Currently amended) A monoclonal antibody or a functional fragment thereof, ~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms, ~~and which~~ binds to TRAIL-R2, and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody or [[and]]the functional fragment thereof, and wherein the

survival rate of said carcinoma cells in the following test using the said antibody is 80% or less,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which are colon carcinoma cells, at a concentration of 5 x 10^4/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the antibody or the functional fragment thereof which is bound binds to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that the concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing at 37°C under 5.0% carbon dioxide gas for 1 hour, adding a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells such that the concentration is 100μg/ml, adding goat anti-human IgG (γ)-specific polyclonal antibodies at a final concentration of 10μg/ml, culturing each well at 37°C under 5.0% carbon dioxide gas for 2 days, washing each well once with PBS and adding fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQUEOUS Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) as well as a carcinoma cell-free well and a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody which binds to TRAIL-R2 and does not bind to the carcinoma cells using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is ~~calculates~~ calculated using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing said carcinoma cells tested, "b" represents the measured value of a carcinoma cell-free well, and "c" represents the measured value of a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells).

75. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 74, wherein the survival rate is 60% or less.

76. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 74, wherein the survival rate is 40% or less.

77. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 74, wherein the survival rate is 20% or less.

78. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 74, wherein the survival rate is 10% or less.

79. (Currently amended) A monoclonal antibody or a functional fragment thereof, ~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms, ~~and which~~ binds to TRAIL-R2, and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody or [[and]]the functional fragment thereof, and wherein the survival rate of said carcinoma cells in the following test using the said antibody is 80% or less,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which are colon carcinoma cells, at a concentration of 5 x 10^4/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the antibody or the functional fragment thereof which is bound binds to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that the concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing at 37°C under 5.0% carbon dioxide gas for 1 hour, adding a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cell such that the concentration is 3μg/ml, adding goat anti-human IgG (γ)-specific polyclonal antibodies at a final concentration of 10μg/ml, culturing each well at 37°C under 5.0% carbon dioxide gas for 2 days, washing each well once with PBS and adding fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ_{UEOUS} Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) as well as a carcinoma cell-free well and a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody which binds to TRAIL-R2 and does not bind to the carcinoma cells using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is ~~calculates~~ calculated using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing said carcinoma cells, "b" represents the measured value of a carcinoma cell-free well, and "c" represents the measured value of a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells).

80. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 79, wherein the survival rate is 60% or less.

81. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 79, wherein the survival rate is 40% or less.

82. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 79, wherein the survival rate is 20% or less.

83. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 79, wherein the survival rate is 10% or less.

84. (Currently amended) A monoclonal antibody or a functional fragment thereof, ~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms and ~~which~~ binds to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody or [[and]]the functional fragment thereof, and the survival rate of said carcinoma cells is 80% or less on condition that (1)1.0 x 10^5/ml of said carcinoma cells and (2) 1000ng/ml of the antibody or the functional fragment thereof are cultured at 37°C under 5.0% carbon dioxide gas for 48 hours.

85. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 84, wherein the survival rate is 60% or less.

86. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 84, wherein the survival rate is 40% or less.

87. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 84, wherein the survival rate is 20% or less.

88. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 84, wherein the survival rate is 10% or less.

89. (Currently amended) A monoclonal antibody or a functional fragment thereof, ~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms and ~~which~~ binds to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2 independently of exogenous factors other than the antibody or [[and]]the functional fragment thereof, and the survival rate of said carcinoma cells is 80% or less on condition that (1) 5×10^4/ml of said carcinoma cells, (2) 1000ng/ml of the antibody, (3) 100μg/ml of a control antibody or a functional fragment thereof which is the same subclass as the antibody or the functional fragment thereof bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells and (4)an antibody which binds to both the antibody or the functional fragment thereof bound which binds to TRAIL-R2 and the control antibody are cultured at 37°C under 5.0% carbon dioxide gas for 48 hours.

90. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 89, wherein the survival rate is 60% or less.

91. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 89, wherein the survival rate is 40% or less.

92. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 89, wherein the survival rate is 20% or less.

93. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 89, wherein the survival rate is 10% or less.

94. (Currently amended) A monoclonal antibody or a functional fragment thereof, ~~which is a single substance without forming a polymer~~ wherein said antibody or functional fragment thereof is free of any polymeric forms and ~~which~~ binds to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody or [[and]]the functional fragment thereof, and the survival rate of said carcinoma cells is 80% or less on condition that (1)5×10^4/ml of said carcinoma cells, (2)1000ng/ml of the antibody, (3)3μg/ml of a control antibody or a functional fragment thereof which is the same subclass as the antibody or the functional fragment

thereof bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells and (4)an antibody which binds to both the antibody or the functional fragment thereof bound which binds to TRAIL-R2 and the control antibody are cultured at 37°C under 5.0% carbon dioxide gas for 48 hours.

95. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 94, wherein the survival rate is 60% or less.

96. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 94, wherein the survival rate is 40% or less.

97. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 94, wherein the survival rate is 20% or less.

98. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 94, wherein the survival rate is 10% or less.

99. (Previously presented) The monoclonal antibody or the functional fragment thereof of claim 94, wherein the carcinoma cell is Colo205.

100. (Currently amended) An antibody or a functional fragment thereof ~~which is a single substance without forming a polymer, binding and which~~ wherein said antibody or functional fragment thereof is free of any polymeric forms and ~~which~~ binds to TRAIL-R2 according to claim 63, the activity of inducing apoptosis of which the antibody or the functional fragment thereof on carcinoma cells expressing TRAIL-R2 does not substantially change depending on the presence or absence of an antibody which is bound binds to a constant region of the said antibody or the functional fragment thereof which is bound binds to TRAIL-R2.

101. (Currently amended) An antibody or a functional fragment thereof ~~which is a single substance without forming a polymer, binding and which~~, wherein said antibody or functional fragment thereof is free of any polymeric forms and binds to TRAIL-R2 according to claim 64, wherein the survival rate of carcinoma cells expressing TRAIL-R2 does not substantially change depending on the presence or absence of an antibody which is bound

binds to a constant region of the said antibody or the functional fragment thereof which is bound binds to TRAIL-R2.

102. (Previously presented) A therapeutic composition, comprising as an active ingredient the antibody or the functional fragment thereof of claim 63.

103. (Currently amended) A ~~prophylactic or~~ therapeutic agent against tumors, comprising as an active ingredient the antibody or the functional fragment thereof of claim 63.

104. (Currently amended) The ~~prophylactic or~~ therapeutic agent against tumors of claim 103, wherein the tumor is any one tumor selected from the group consisting of colon cancer, colorectal cancer, lung cancer, breast cancer, brain tumor, malignant melanoma, renal cell carcinoma, bladder cancer, leukemia, lymphomas, T cell lymphomas, multiple myeloma, gastric cancer, pancreas cancer, cervical cancer, endometrial carcinoma, ovarian cancer, esophageal cancer, liver cancer, head and neck squamous cell carcinoma, cutaneous cancer, urinary tract carcinoma, prostate cancer, choriocarcinoma, pharyngeal cancer, laryngeal cancer, thecomatosis, androblastoma, endometrium hyperplasy, endometriosis, embryoma, fibrosarcoma, Kaposi's sarcoma, hemangioma, cavernous hemangioma, angioblastoma, retinoblastoma, astrocytoma, neurofibroma, oligodendroglioma, medulloblastoma, ganglioneuroblastoma, glioma, rhabdomyosarcoma, hamartoblastoma, osteogenic sarcoma, leiomyosarcoma, thyroid sarcoma, and Wilms tumor.

105.-107. (Canceled)

108. (Currently amended) A method of producing the monoclonal antibody of claim 63, which comprises,

(i) a step of immunizing an animal with TRAIL-R2 or an extracellular fragment thereof, cells expressing the TRAIL-R2 or an extracellular fragment thereof~~, or a DNA containing the gene encoding all or a part of the extracellular domain of TRAIL-R2~~,

(ii) a step of obtaining monomeric monoclonal antibodies from the animal, wherein the monomeric monoclonal antibodies induce apoptosis;

(iii) a step of evaluating the activity of the monomeric monoclonal antibody which ~~is a single substance without forming a polymer, binding and which~~ binds to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody,

(iv) a step of separating the monoclonal antibody which is a single substance without forming a polymer and which binds to TRAIL-R2, from the antibody,

(v) a step of evaluating the activity of inducing apoptosis of the said monomeric monoclonal antibody, and

(vi) a step of selecting the monoclonal antibody having the activity of inducing apoptosis.

109. (Currently amended) The method of producing the monoclonal antibody of claim 108, wherein step (v) includes the following test to determine a survival rate of carcinoma cell using the antibody,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which are colon carcinoma cells, at a concentration of 1.0×10^5/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the antibody which is bound binds to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that the concentration of the antibody or the functional fragment thereof becomes 1000ng/ml when it is added to each well at 10μl/well, culturing each well at 37°C under 5.0% carbon dioxide gas for 48 hours, washing each well once with PBS and adding fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQ$_{UEOUS}$ Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) as well as a carcinoma cell-free well and a well containing said carcinoma cells and a control antibody which does not bind to said carcinoma cells and is the same subclass as the antibody or the functional fragment thereof which binds to TRAIL-R2, or well containing said carcinoma cells and a control antibody which does not bind to the carcinoma cells and does not have a constant region using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is ~~calculates~~ calculated using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing said carcinoma cells and the antibody or the functional fragment thereof, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents (i) the measured value of the absorbance of a well containing said carcinoma cells and a control antibody which does not bound bind to said carcinoma cells and is the same subclass as the antibody or the functional fragment thereof bound which binds to TRAIL-R2 when the antibody or the functional fragment thereof has a constant region, or (ii) the measured value of a well containing said carcinoma cells and a control antibody which does not bound bind to said carcinoma cells and does not have a constant region when the antibody or the functional fragment thereof does not have a constant region),

and

(5) Selecting the antibody having which results in the survival rate of the cells of 80% or less is selected.

110. (Currently amended) The method of producing the monoclonal antibody of claim 108, wherein step (v) includes the following test to determine a survival rate of carcinoma cell using the antibody,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which are colon carcinoma cells, at a concentration of 1.0 x 10^5/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the monoclonal antibody which is bound binds to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that the concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing each well at 37°C under 5.0% carbon dioxide gas for 48 hours, washing each well once with PBS and adding fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQUEOUS Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) as well as a carcinoma cell-free well and a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody which binds to TRAIL-R2 and does not bind to the carcinoma cells using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is ~~calculates~~ calculated using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing said carcinoma cells and the antibody or the

functional fragment thereof, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents the measured value of the absorbance of a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells),

and

(5) Selecting the antibody having which results in the survival rate of the cells of 80% or less is selected.

111. (Currently amended) The method of producing the monoclonal antibody of claim 108, wherein step (v) includes the following test to determine a survival rate of carcinoma cell using the antibody,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which are colon carcinoma cells, at a concentration of 5 x 10^4/ml in RPMI-1640 medium containing 10% FCS, adding the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the antibody which is bound binds to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that the concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing at 37°C under 5.0% carbon dioxide gas for 1 hour, adding a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells such that the concentration is 100μg/ml, adding goat anti-human IgG (γ)-specific polyclonal antibodies at a final concentration of 10μg/ml, culturing each well at 37°C under 5.0% carbon dioxide gas for 2 days, washing each well once with PBS and adding fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQUEOUS Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) as well as a carcinoma cell-free well and a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody which binds to TRAIL-R2 and does not bind to the carcinoma cells using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is ~~calculates~~ calculated using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing said carcinoma cells and the antibody or the functional fragment thereof, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents the measured value of the absorbance of a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells),

and

(5) Selecting the antibody having which results in the survival rate of the cells of 80% or less is selected.

112. (Currently amended) The method of producing the monoclonal antibody of claim 108, wherein step (v) includes the following test to determine a survival rate of carcinoma cell using the antibody,

said test comprising the following steps:

(1) Preparing Colo205 cells (ATCC No.CCL-222) which are colon carcinoma cells, at a concentration of 5 x 10^4/ml in RPMI-1640 medium containing 10% FCS, adding

the cells to each well of a 96-well flat-bottomed plate at 100μl/well and culturing at 37°C under 5.0% carbon dioxide gas for 24 hours,

(2) Adding to each well of (1) the monoclonal antibody which is bound binds to TRAIL-R2 dissolved in RPMI-1640 medium containing 10% FCS such that the concentration of the antibody becomes 1000ng/ml when it is added to each well at 10μl/well, culturing at 37°C under 5.0% carbon dioxide gas for 1 hour, adding a control antibody which is the same subclass as the antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cell such that the concentration is 3μg/ml, adding goat anti-human IgG (γ)-specific polyclonal antibodies at a final concentration of 10μg/ml, culturing each well at 37°C under 5.0% carbon dioxide gas for 2 days, washing each well once with PBS and adding fresh RPMI-1640 medium containing 10% FCS at 100μl/well,

(3) Adding 20 μl of MTS reagent (Cell Titer 96® AQUEOUS Non-Radioactive Cell Proliferation Assay: Promega) to each well of (2) and culturing at 37°C under 5.0% carbon dioxide gas for 2 hours, and

(4) Measuring absorbance of each well of (3) at a wavelength of 490 nm (with a reference wavelength of 630 nm) as well as a carcinoma cell-free well and a well containing said carcinoma cells and a control antibody which is the same subclass as the antibody which binds to TRAIL-R2 and does not bind to the carcinoma cells using a microplate reader and calculating the survival rate of the cells using the reducibility of the mitochondria as an indicator,

wherein the survival rate of the cells is ~~calculates~~ calculated using the following formula,

Survival rate (%) = 100 × (a-b)/(c-b) (wherein "a" represents the measured value of the absorbance of a well containing said carcinoma cells and the antibody or the functional fragment thereof, "b" represents the measured value of the absorbance of a carcinoma cell-free well, and "c" represents the measured value of the absorbance of a well containing said carcinoma cells and a control antibody which is the same subclass as the

antibody bound which binds to TRAIL-R2 and does not bound bind to said carcinoma cells), and

(5) Selecting the antibody having which results in the survival rate of the cells of 80% or less is selected.